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Anti-seizures therapeutics in patients with epilepsy: an approach to levetiracetam – review

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Abstract

Epilepsy is a chronic condition that consists of a transient disorder of brain function manifested by recurrent and unprovoked seizures affecting approximately 50 million people worldwide. Antiepileptic treatment is aimed at possible improvement the quality of life by reducing epilepsy seizures with the lowest possible side effects. One of the newest broad spectrum antiepileptic drug (AED) for the treatment of wide range of epilepsies – focal, partial, myoclonic, tonic-clonic and primary generalized seizures that can be used in both children and adults is levetiracetam. Levetiracetam is believed to bind to SV2A (synaptic vesicle protein 2A) in the brain, prevent the release of calcium stores from neurons and inhibit GABA and glycine activity. Due to the unique mechanism of action, high bioavailability (in both oral and intravenous administration), rapid absorption, metabolism based on the hydrolysis of acetamide groups in the blood (independent of the liver) and the lack of activity of the resulting metabolites, the drug is considered to be safe and effective in reducing and stopping seizures.

In this review, we present the latest reports on the effectiveness of levetiracetam and its potential in the treatment of epilepsy in children and adults.

Key words: epilepsy; levetiracetam; seizures; therapeutics; treatment; drug resistance

Introduction

Epilepsy is a chronic condition that consists of a transient disorder of brain function manifested by recurrent and unprovoked seizures. During a seizure, the nerve cells experience excessive and spontaneous bioelectric discharges [1]. Status epilepticus (SE) - that is, repetitive seizures at short intervals or for prolonged duration, can have permanent consequences such as damage to neurons and changes in neural networks [2]. WHO (World Health Organization) estimates that about 50 million people worldwide have epilepsy, which is nearly 0.7% of the population [3]. According to Fiest et al. the frequency of epilepsy is 61.4 per 100,000 person-years [4]. The rate is higher in low- and middle-income countries and highest in the lowest social classes (≈80%) [2,3]. According to ILAE (The International League Against Epilepsy), epilepsy is defined as two unprovoked (or reflex) seizures occurring more than 24h apart; a single unprovoked (or reflex) seizure if recurrence risk is high (> 60% over the next 10 years); or a diagnosis of an epilepsy syndrome (based on clinical presentation, encephalography - EEG and additional examinations) [5,6].

ILAE classifies seizures according to the type into focal, generalized, or unknown (depending on the onset). A more precise division divides focal seizures into those with retained awareness and impaired awareness and further into motor seizures (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic) and non-motor seizures (autonomic, behaviour arrest, cognitive, emotional, sensory); generalized seizures can be divided only into motor seizures (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms) and non-motor (also known as absence) seizures (typical, atypical, myoclonic, eyelid myoclonia). Seizures of unknown onset can be classified into motor seizures (tonic-clonic, epileptic spasms) and non-motor seizures (behaviour arrest). Combined epilepsy (with both general and focal seizures) includes Dravet or Lennox-Gastaut syndrome [6,7]. Active epilepsy is the condition that is treated regularly with medication or has occurred within the last 5 years [2]. Cured epilepsy is considered when seizures are absent for more than 10 years, with at least 5 years without taking antiepileptic drugs [8].

Due to the etiology, ILAE divides the etiology of epilepsy into six categories: structural, genetic, infectious, metabolic, immunological and unknown [6,9]. Balestrini et al. also distinguish a neurodegenerative etiology [9].

The diagnosis of epilepsy is based on patient interview and history - age of seizures onset, nature of seizures, comorbidities; EEG and additional neuroimaging tests [7]. The identification of pathological changes in the brain correlating with the clinical manifestation of the seizure and / or an abnormal EEG recording of changes typical for epilepsy (spikes and sharp waves; spike-slow wave complexes) are important in the diagnosis of the disease and making the appropriate therapeutic decision. In about 21-37% of patients with epileptic seizures, focal changes are detected in neuroimaging tests. The percentage is higher in people with drug-resistant focal epilepsy. Magnetic resonance imaging (MRI) is the method of choice that allows visualization of focal lesions (which may be invisible on CT), but if there are contraindications, computed tomography (CT) with contrast is recommended. EEG, considered as the most important tool in the diagnosis of epilepsy, is the only test so far that can show paroxysmal bioelectric activity of the brain. This test can be supportive in classifying the types of seizures, epilepsy syndromes and also to assess recurrence risk - the presence of epilepsy-specific changes in a concrete area of the brain may suggest the location of the epilepsy area. However, it should be remembered that the correct EEG recording does not preclude the diagnosis of epilepsy. More accurate diagnostics include video-EEG and electrocorticography [6,8,10]. According to Weber et al. genetic testing plays an important role in the diagnosis of epilepsy - approximately 500 epilepsy-related genes have been detected, which increased the chances of identifying the causes of some types of epilepsy [11,12].

Antiepileptic treatment is aimed at possible improvement the quality of life by reducing epilepsy seizures with the lowest possible side effects. It is estimated that the use of drugs allows for remission of seizures in about 65-80% of people with epilepsy [6,13]. The drugs used should be adjusted to age, sex, reproductive capacity, comorbidities, seizure type, drug interactions and hypersensitivity - therefore the individualization of the treatment method plays a significant role. Antiepileptic drugs can be used as monotherapy and polytherapy, however, due to the risk of toxicity, monotherapy seems to be the more advantageous option. Treatment is started with a low dose of an anti-epileptic drug which should be gradually increased to the lowest possible maintenance dose, although it is estimated that approximately 50% achieve seizure remission at the initial dose. This effect is intended to reduce side effects, but a higher dose may be given in the event of frequent seizures or status epilepticus [6,8,13]. Drug-resistant

epilepsy is epilepsy treated with at least two well-chosen drugs (in mono or polytherapy) in order to obtain a permanent absence of seizures. It is estimated that it may affect about 25-35% of patients and then surgery and neurostimulatory interventions (also vagal nerve stimulation) should be considered [6,8,14,15].

Here we present the latest reports on the effectiveness of levetiracetam and its potential in epilepsy patients.

Research on the effectiveness of levetiracetam

Levetiracetam (LEV) approved by the FDA in 2000 is one of the newest broad spectrum antiepileptic drug (AED) for the treatment of wide range of epilepsies - partial, myoclonic and tonic-clonic seizures that can be used in both children and adults. Initially, it was approved in US as adjunctive therapy for partial-onset seizures. Further research allowed the use of the drug for the treatment of focal, myoclonic and primary generalized seizures – at first only in an oral form, but since 2006, intravenous use has been allowed in patients over 15 years of age with oral intolerance. In Europe, levetiracetam is used in mono and polytherapy for partial seizures (one month or older), tonic-clonic seizures (over five years old) and myoclonic seizures (in people aged 12 and over) [16,17,18]. It can be used as first-line therapy in patients with epilepsy [19].

The mechanism of levetiracetam is not fully understood. Levetiracetam is believed to bind to SV2A (synaptic vesicle protein 2A) in the brain, prevent the release of calcium stores from neurons and inhibit GABA and glycine activity [20,21]. The bioavailability of the oral drug is almost 100% - the drug is quickly absorbed and reaches its maximum concentration 1 hour after taking it (however, the maximum concentration is reduced by 20% when taken with food). Levetiracetam is not metabolised in the liver - it is broken down by hydrolysis of the acetamide group in blood and 66% of the drug is excreted unchanged via the kidneys (however, the dose should be adjusted according to creatinine clearance). The metabolites formed during the transformation are inactive. Protein binding is less than 10% which has no significant clinical effect. The half-life of levetiracetam is 6-8 hours and in elderly is increased by 40% (lower creatinine clearance). In infants and older children, this period is shortened and amounts to 5-6 hours, in newborns, due to the higher creatinine clearance than in adults, it is 9 hours. The oral and intravenous bioavailability is comparable [18,22,23,24].

Cao et al. assessed the efficacy and safety of levetiracetam in children up to 18 years of age with focal seizures using a meta-analysis. The effective treatment was considered to be

when the number of seizures was reduced by at least 50% from the baseline value, while the drug safety assessment was performed using TEAE rate (treatment-emergent adverse events) - the percentage of patients who experienced at least one adverse event (also ADR-related with TEAE - adverse drug related reactions), as well as dropout rate (due to any nuisance reasons) and recall rate (due to nuisance side effects). The study showed that levetiracetam was more effective than placebo. The median seizure reduction rate was 55% (31-79%). The ORR (overall response rates) for at least one TEAE indicator was 74% (54–94%) and for at least one TEAE indicator related to ADR was 48% (40–55%). The RRs for withdrawal rate were 0.77 (0.44-1.38) and ORRs were 17% (5%-28%); the ADR-related withdrawal rate were 0.91 (0.42-1.98) and ORRs were 6% (4%-8%).The most common adverse events were fever, headache, nervousness, and somnolence. The analysis showed that levetiracetam is a good treatment option for children with partial seizures due to its high efficacy in reducing seizures as well as its low toxicity compared to other AEDs [25].

McHugh et al. compared the efficacy of phenobarbital (used in the first instance in neonatals with epileptic seizures despite its relatively high toxicity - impaired neurocognitive and motor development in neonates) and levetiracetam (not yet approved for this use). The effectiveness was assessed on the basis of the reduction of seizures - here, in the case of primary levetiracetam, 77% seizure cessation was obtained, in the case of secondary levetiracetam - 63%, and in the case of the originally used phenobarbital - 46%. According to researchers, levetiracetam may be more effective than phenobarbital in reducing seizures, with significantly lower toxicity [26]. Penner et al. think that levetiracetam seems to be a promising alternative to phenobarbital used in epilepsy in neonates, also due to its neuroprotective effect and good safety profile. However, more long-term studies on neonatals are needed to make this drug a first-line drug [27].

Nolan et al. tested the effectiveness of levetiracetam in absentee seizures in children. However, this medicine was only effective in about a quarter of the patients. In 74% of subjects, treatment with levetiracetam was discontinued because seizures and occurring (intolerable) side effects were not fully controlled. Studies have shown that even a low dose in people who are effective in levetiracetam can reduce a seizure [28].

Manreza et al. conducted a phase 3, multicentre, randomized, double-blind study in 114 people aged 4-65 years who were treated with levetiracetam as adjuvant treatment in refractory epilepsy - in whom, despite the treatment, there were at least 12 in the last year seizures. The effectiveness of 16 weeks of treatment was assessed on the basis of a reduction in the number

of focal seizures per week by 50% and more. Participants were randomized to receive placebo (control group - 55 people) or levetiracetam (59 people) which was increased every 2 weeks from 20 mg/kg/day or 1000mg/day up to 60 mg/kg/day or 3000mg/day. The study showed high efficiency and safety in both children and adults - The results of the study showed a much greater effectiveness of levetiracetam than placebo (reduction in the number of seizures by 38.7% of patients in the research group and 14.3% in the control group); Moreover, the study demonstrated a high safety profile of levetiracetam, and the incidence of adverse events was comparable to placebo (levetiracetam - 69.1%, placebo - 52.4%), and no clinically significant changes in vital signs were observed. In the study, the most effective and safe dose of levetiracetam was 1000-3000 mg/day or 60 mg/kg/day (in children). Based on the results of the study, scientists conclude that the implementation of levetiracetam should be considered in refractory focal epilepsy - in both children and adults [29].

Marson et al. conducted a randomized study (SANAD II) on the long-term efficacy of levetiracetam and zonisamide compared to lamotrigine in newly diagnosed focal epilepsy (as first-line treatment). 990 participants aged 5 years and older (mean age - 39.3 years) were randomly assigned to one of the three groups (levetiracetam - 332 people, zonisamide - 328 people, lamotrigine - 330 people) - patients, however, were aware of what drug they were receiving. Initial dosages for ages 12 and over included oral lamotrigine 50mg in the morning and 100mg in the evening, 500mg levetiracetam twice daily, and 100mg zonisamide twice daily. People under the age of 12 received lamotrigine 1.5 mg / kg twice daily, levetiracetam 20 mg / kg twice daily and zonisamide 2.5 mg / kg twice daily. Adverse events occurred in 33% of patients using lamotrigine (the most common were neurological disorders - 16%, psychiatric disorders - 13%, gastrointestinal disorders - 8%), 44% - levetiracetam (here in 30% psychiatric disorders, neurological disorders in 17% , general disorders in 10%) and 45% zonisamide (here psychiatric disorders in 23%, neurological disorders in 19%, general disorders in 12%). Moreover, side effects of levetiracetam caused anxiety, depression and stigma much more often than other drugs. 37 people died during the study - however, nothing indicated a higher rate when using a particular drug. In terms of effectiveness and profitability, lamotrigine turned out to be the best - therefore, according to scientists, in focal epilepsy, it should still be used as a first-line drug despite recommendations for the use of lamotrigine and zonisamide as monotherapy in the world. According to the researchers, the results of the study are all the more important due to the frequent prescription of levetiracetam to patients with epilepsy by neurologists [30].

A study by Ballve et al. investigated the effectiveness of levetiracetam monotherapy in women of reproductive age (17-43 years; mean - 25.4 years) with idiopathic generalized epilepsy - IGE. The observation period ranged from 24 to 120 months (mean - 68.3 months). Of the 26 women in the study, 11 continued to take levetiracetam (of which 10 had no seizures anymore and 3 had no seizures after stopping treatment). Change of treatment was necessary in 12 patients - no efficacy in 3, side effects in 5, both factors in 4. In 3 people, despite the use of levetiracetam in polytherapy, no efficacy in reducing seizures was noticed. The most common side effects of levetiracetam in the study group were irritability, drowsiness, mood disturbances and sedation. The study suggests that levetiracetam may be a good first-line treatment option in women of childbearing age with IGE. The researchers point out that the numerous side effects that have been shown in their study may limit the use of this drug. However, the confirmation of the scientists' results requires research on a larger group of people [31].

Lyttle et al. compared the efficacy and safety of intravenous phenytoin - previously used in the UK as a second-line treatment for status epilepticus in children aged 6 months to 18 years, compared to levetiracetam based on a randomized study. Phenytoin was administered as an intravenous infusion of 20 mg/kg over 20 minutes (134 patients) and levetiracetam at a dose of 40 mg/kg for at least 5 minutes (152 patients). Seizure status epilepticus was terminated in 64% of children in the phenytoin group and in 70% of children receiving levetiracetam. There were no significant changes in the timing of administration or seizure termination between both drugs. The results showed a slightly higher effectiveness of levetiracetam in stopping a seizure, however, due to the better safety profile of levetiracetam compared to phenytoin (in this study phenytoin showed severe, life-threatening hypotension in one patient), levetiracetam should be considered as an alternative to the more toxic phenytoin. The researchers point out that the known side effects of phenytoin - apart from hypotension, also arrhythmia and severe extravasation damage are more dangerous than the side effects observed with levetiracetam - sedation, drowsiness, dizziness [32].

A study by Kapur et al. compared the efficacy and safety of intravenous levetiracetam, fosphenytoin and valproate in children and adults who did not respond to benzodiazepine administration in the status epilepticus. The study involved 384 people (39% up to 17 years of age; 48% - from 18 to 65 years of age; 13% - more than 65 years of age) who were randomly assigned to three groups receiving levetiracetam (145 people), fosphenytoin (118 people), and valproate (121 people). Efficacy was assessed on the basis of clinical improvement within 60 minutes of drug administration, while safety was based on the occurrence of life-threatening

side effects. Resolution of status epilepticus and improvement in functioning occurred in 47% of the levetiracetam group, 45% of the fosphenytoin group and 46% of the valproate group. Adverse events occurred in 42% of people - the most incidents of hypotension and the need for intubation occurred in the fosphenytoin group, and the most deaths occurred in the levetiracetam group (although these differences were not significant). The results of the study showed similar efficacy and frequency of side effects of the three drugs used in the study [33].

Conclusions

Based on the presented studies, levetiracetam is often selected as the first-line therapy in the wide-spectrum treatment of epilepsy in children and adults due to its low toxicity and liver-independent metabolism compared to other antiepileptic drugs. However, despite many studies proving the effectiveness and high safety profile of this drug, some studies show numerous side effects of this drug - including depression, sedation and dizziness. The use of levetiracetam in drug resistant epilepsy seems to be promising - research shows the effectiveness of this drug, hence the need for further research.

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